



Indiana
Department
of
Health

LATENT TB INFECTION (LTBI) TREATMENT GUIDELINES

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Disclosures

- Medical Consultant, TB Control Program
Indiana Department of Health
- Have personally endured over 40 Tuberculin skin tests
(either negative or misinterpreted...)

Major thanks to the Indiana Department of Health TB Program for updated statistics and amazing support throughout the year!

Objectives

- Review TB impact on world health
- Contrast TB impact on U.S. and Indiana
- Compare TB disease to latent TB infection (LTBI)
- Overview of LTBI treatments

Global/U.S. TB Burden, 2019

- An estimated 10.0 million new TB disease cases
- 1.2 million deaths due to TB disease (1.2, '18)
 - With 0.20 million deaths from TB among people living with HIV (0.25 last year, 69% drop since 2000)
- The rate of decline remains low at 2.3% per year (2.0%, '18)
 - Not fast enough decline to reach first milestone of End TB Strategy
- Estimated up to 13 million persons in U.S. TB infected
- Incidence rate of U.S. cases, 2.7/100,000, total of 8,916

Sources: WHO Global Tuberculosis Report 2019,
CDC: <https://www.cdc.gov/tb/statistics/default.htm>

TB Epidemiology, Worldwide by regions

- Africa and South-East Asia have the highest TB incidence rates
- Rates shown are cases per 100,000 population

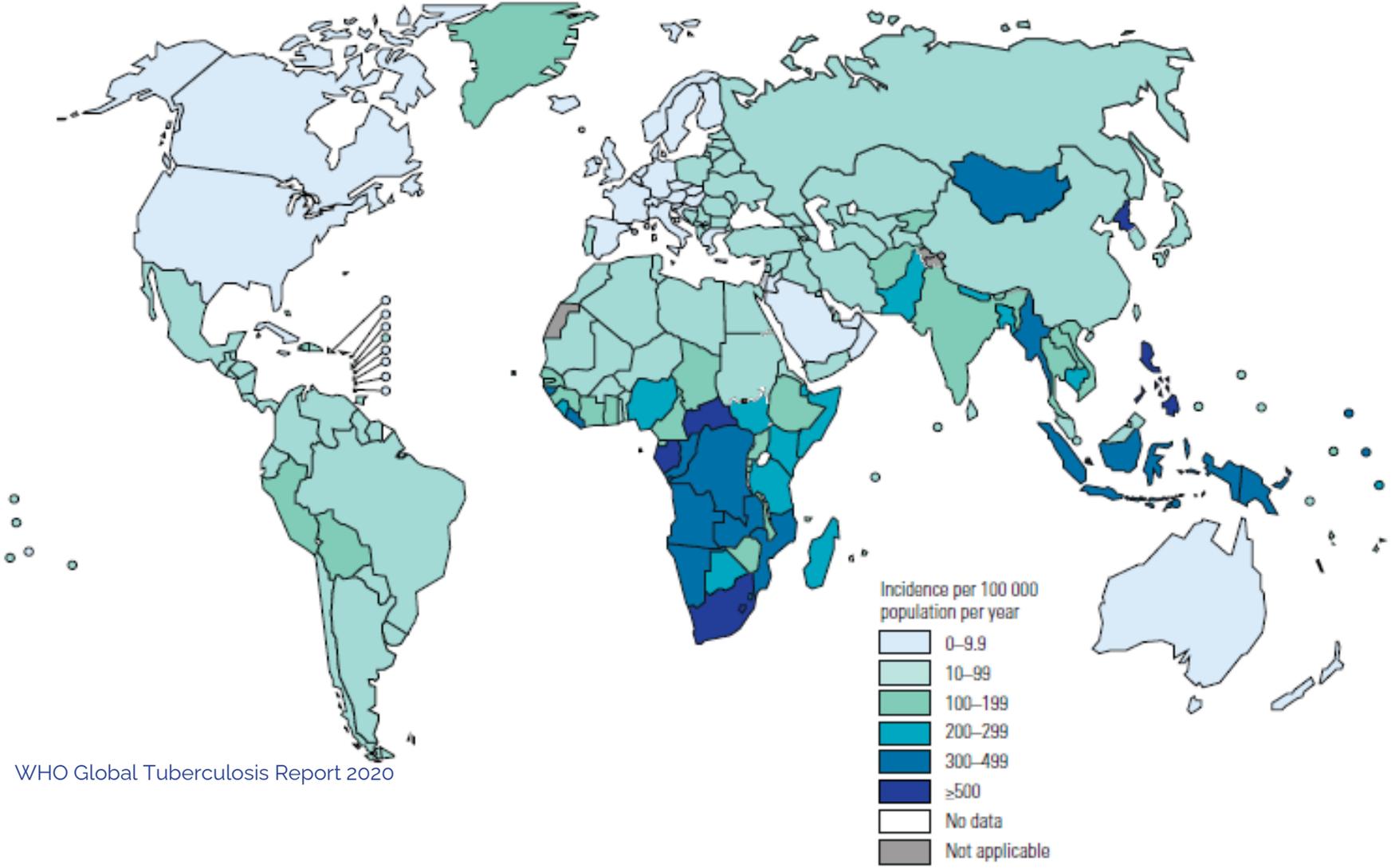
2019	TOTAL TB INCIDENCE	
	BEST ESTIMATE	UNCERTAINTY INTERVAL
High TB burden countries	177	156–198
Africa	226	201–252
The Americas	29	27–31
Eastern Mediterranean	114	90–141
Europe	26	23–30
South-East Asia	217	173–266
Western Pacific	93	77–111
Global	130	116–143

2018	TOTAL TB INCIDENCE	
	BEST ESTIMATE	UNCERTAINTY INTERVAL
High TB burden countries	180	159–202
Africa	231	206–257
Americas	29	27–31
Eastern Mediterranean	115	91–142
Europe	28	24–32
South-East Asia	220	175–271
Western Pacific	96	79–114
GLOBAL	132	118–146

TB Epidemiology, drug-resistant strains

- During 2019, close to half a million people developed rifampicin-resistant TB of which 78% had multi-drug resistant TB
 - Recall that MDR are by definition resistant to INH and rifampin
- Three countries (China, India, and Russian Federation) account for 49% of the global burden
 - Need to be aware of the country of origin, work, or travel to increase suspicion of resistance

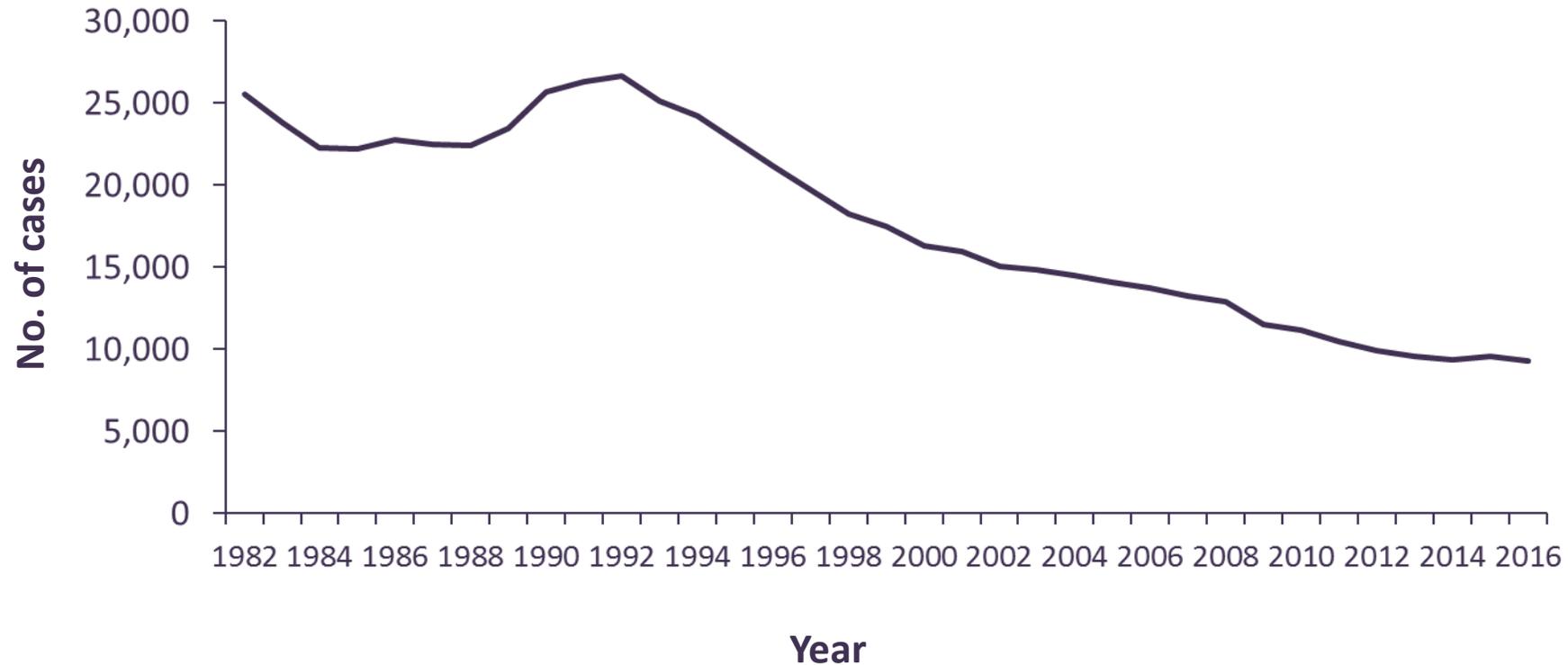
Estimated World TB Incidence Rates, 2019



WHO Global Tuberculosis Report 2020



Reported Tuberculosis (TB) Cases United States, 1982–2016*

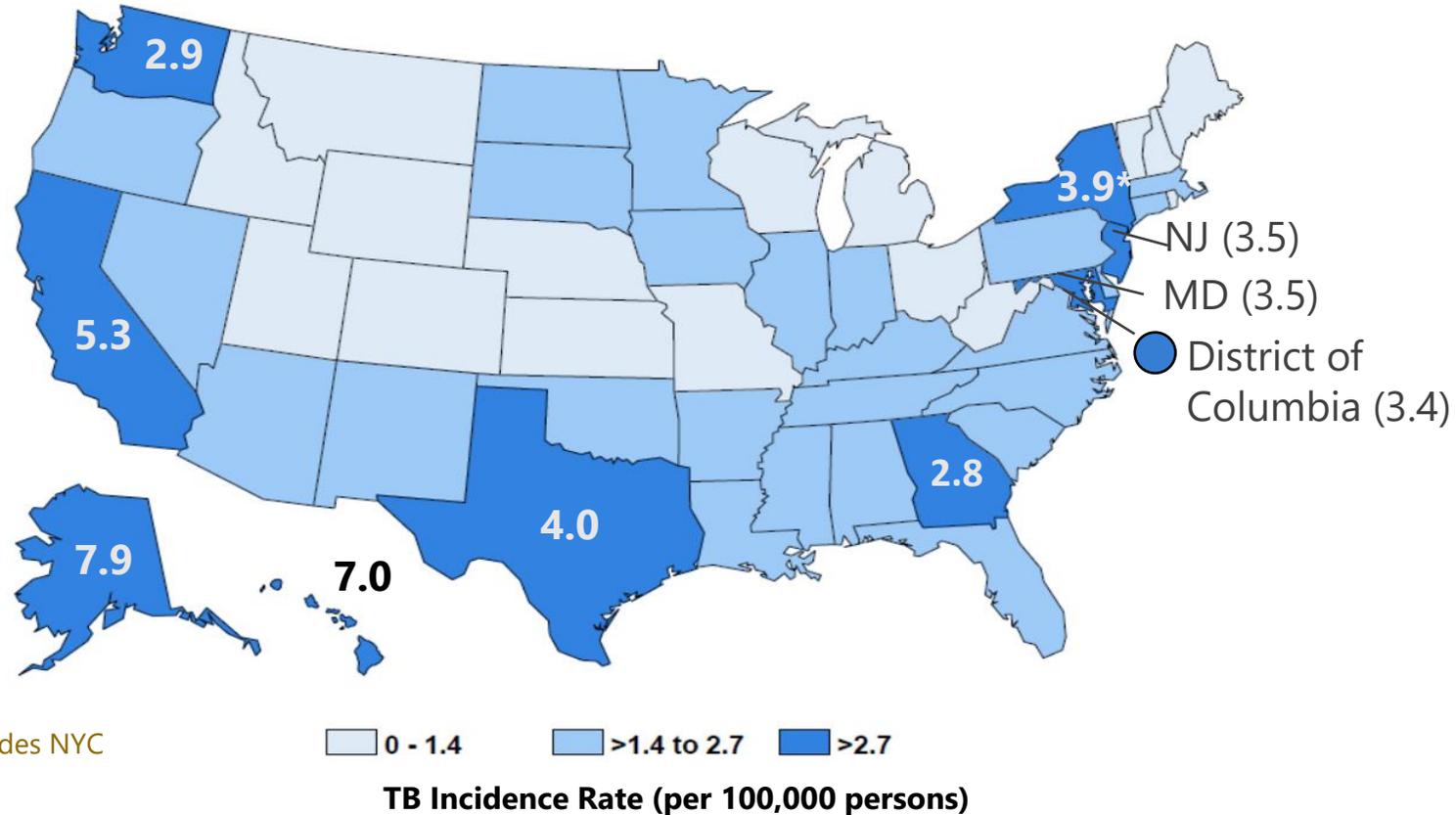


*As of June 21, 2017.

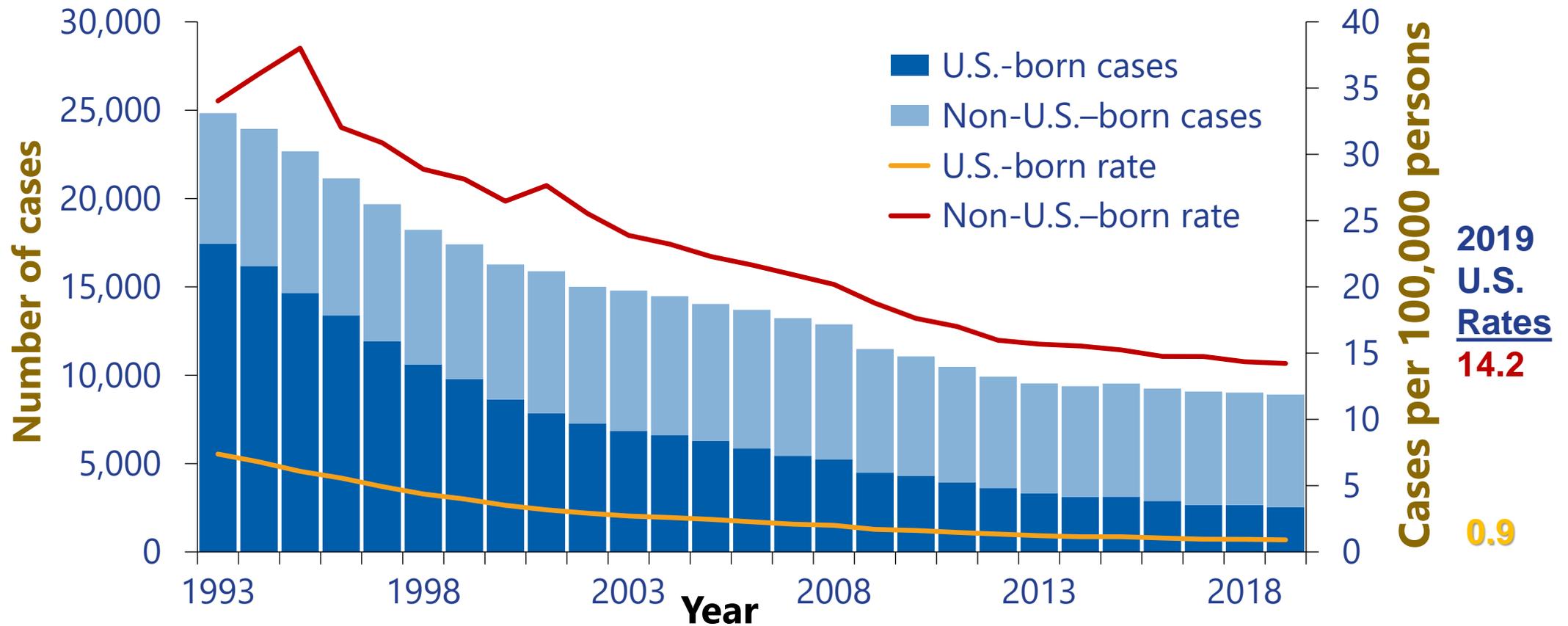
Factors Contributing to the Increase in TB Morbidity: 1985-1992

- Deterioration of the TB public health infrastructure
- HIV/AIDS epidemic
- **Immigration from countries where TB is common**
- Transmission of TB in congregate settings
 - Homeless shelters, prisons, etc.

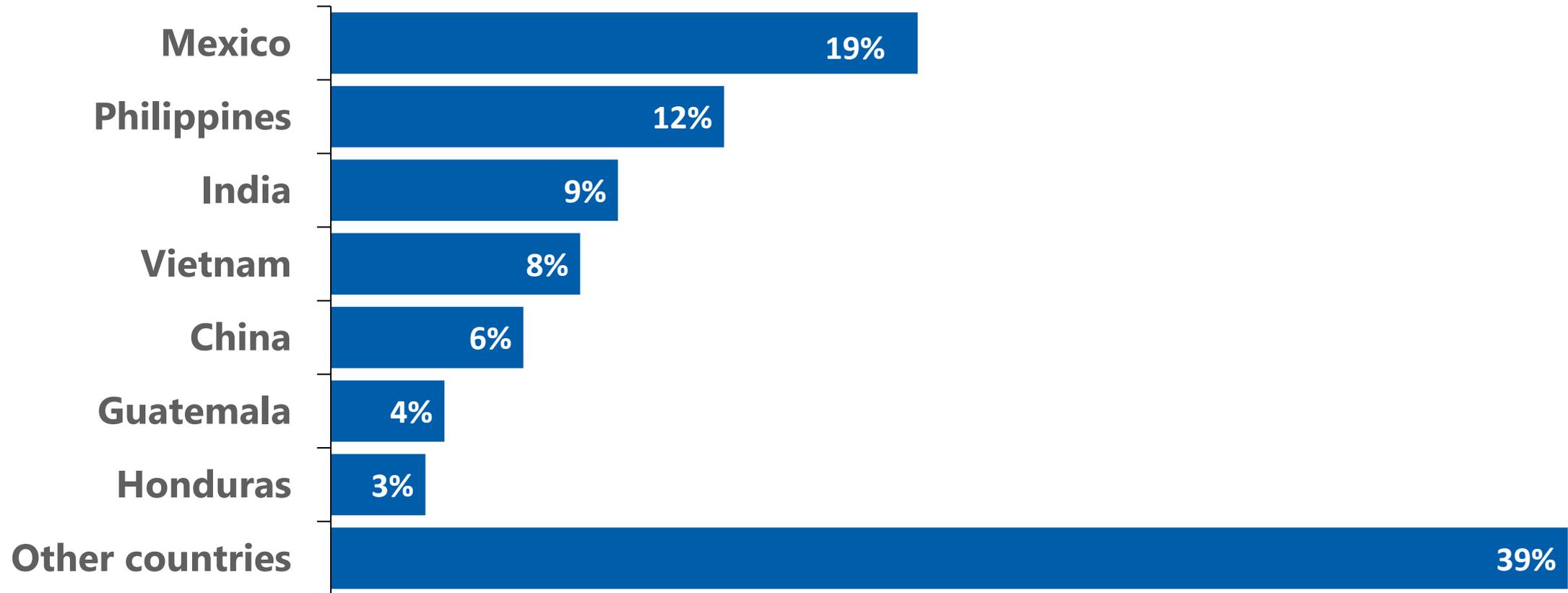
Tuberculosis Case Rates by Reporting Area United States, 2019



TB Cases and Rates Among U.S.-Born versus Non-U.S.-Born Persons, United States, 1993–2019



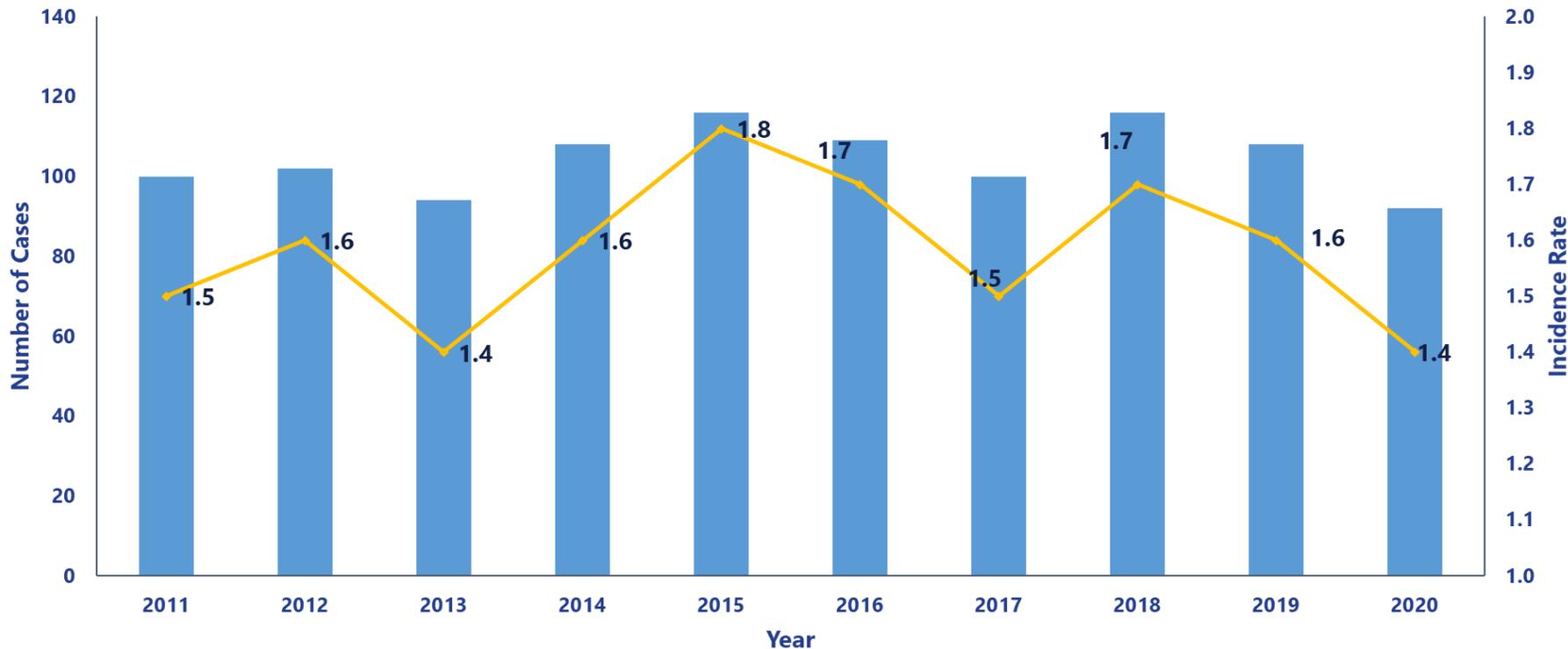
Countries of Birth Among Non-U.S.–Born Persons Reported with TB, United States, 2019



Percentage of TB cases among non-U.S.–born persons

Number of Tuberculosis Cases and Incidence Rate, Indiana, 2011-2020

Indiana TB 10-Year Trend, 2011-2020



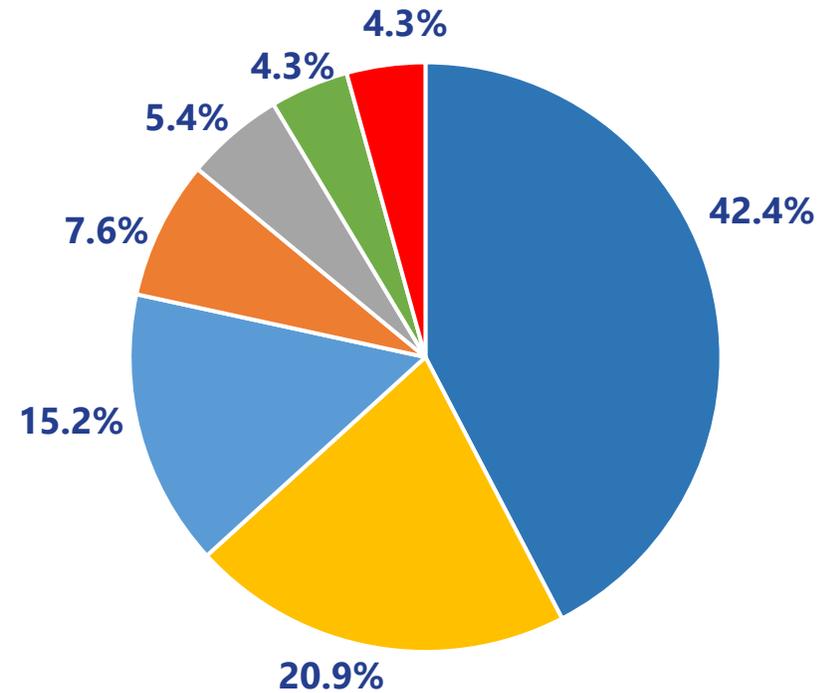
Cases = 92
Incidence Rate
= **1.4**/100,000

Contrast to:
U.S. – 2.7* (**2.8**)
Global – 130**

* Per CDC 2019 TB Data

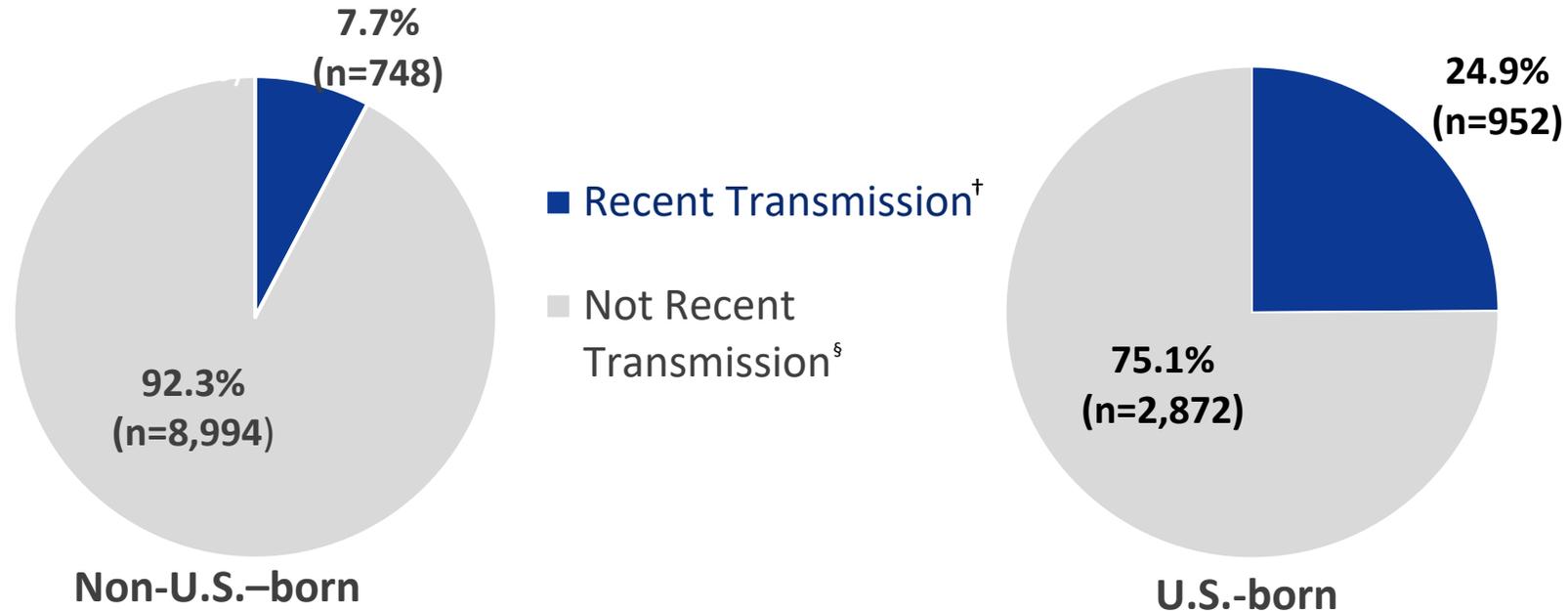
** Per WHO Global TB Report 2020

TB Cases by Country of Birth, Indiana, 2020



N=92

Percentages of Tuberculosis Cases Estimated to be Attributed and Not Attributed to Recent Transmission, by Origin of Birth*, 2018–2019



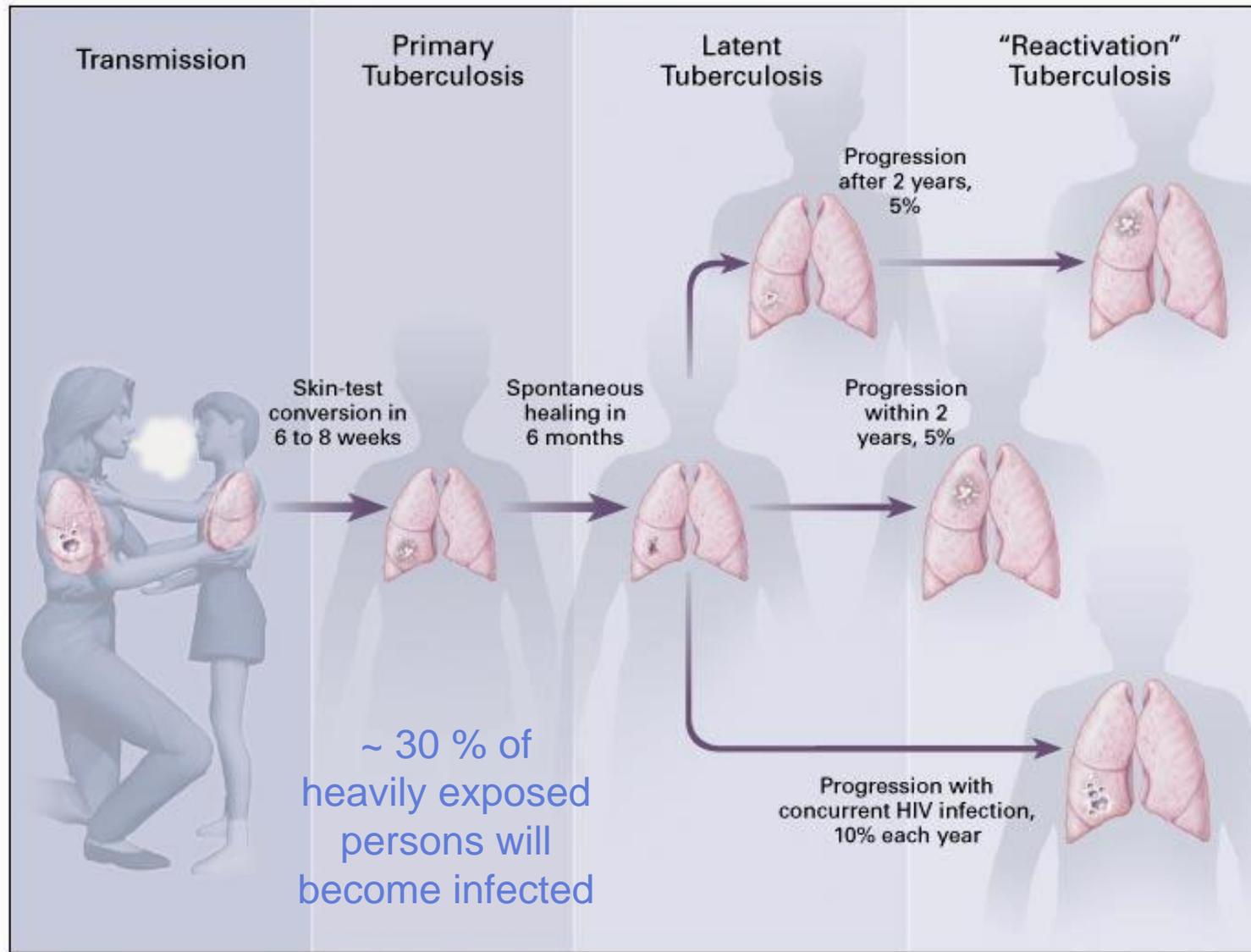
* Cases with unknown origin of birth not shown (n=11).

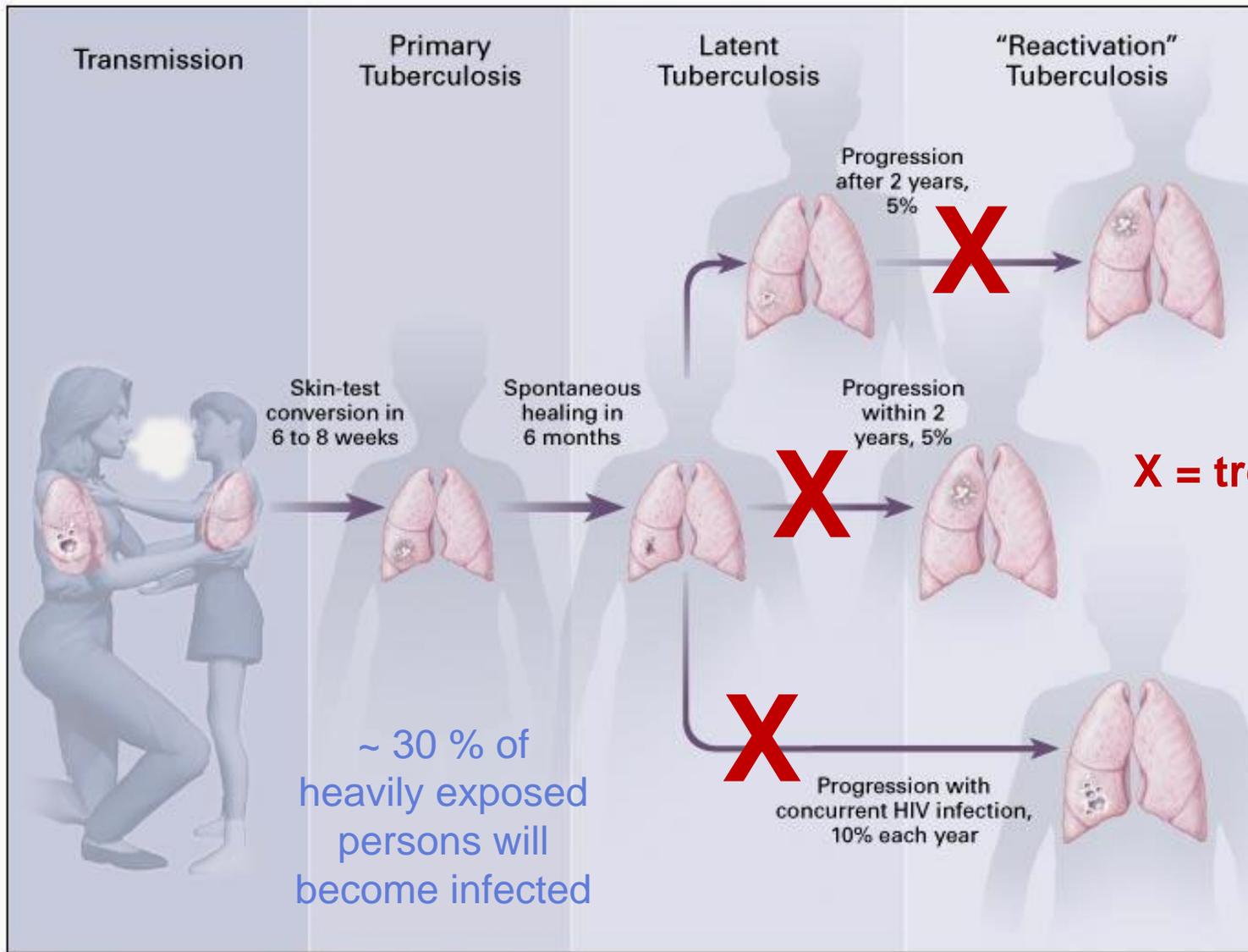
† A TB case is designated as attributed to recent transmission if a plausible source case can be identified in a person who i) has the same *M. tuberculosis* genotype, ii) has an infectious form of TB disease, iii) resides within 10 miles of the TB case, iv) is 10 years of age or older, and v) was diagnosed within 2 years before the TB case.

§ Cases not attributed to recent transmission may be misclassified in children <5 years old or indeterminate in persons with a recent U.S. arrival due to limitations of the plausible-source case method.



This is why we screen and treat Latent TB Infection!
The opportunity to screen is a chance to treat TB.





X = treatment of LTBI

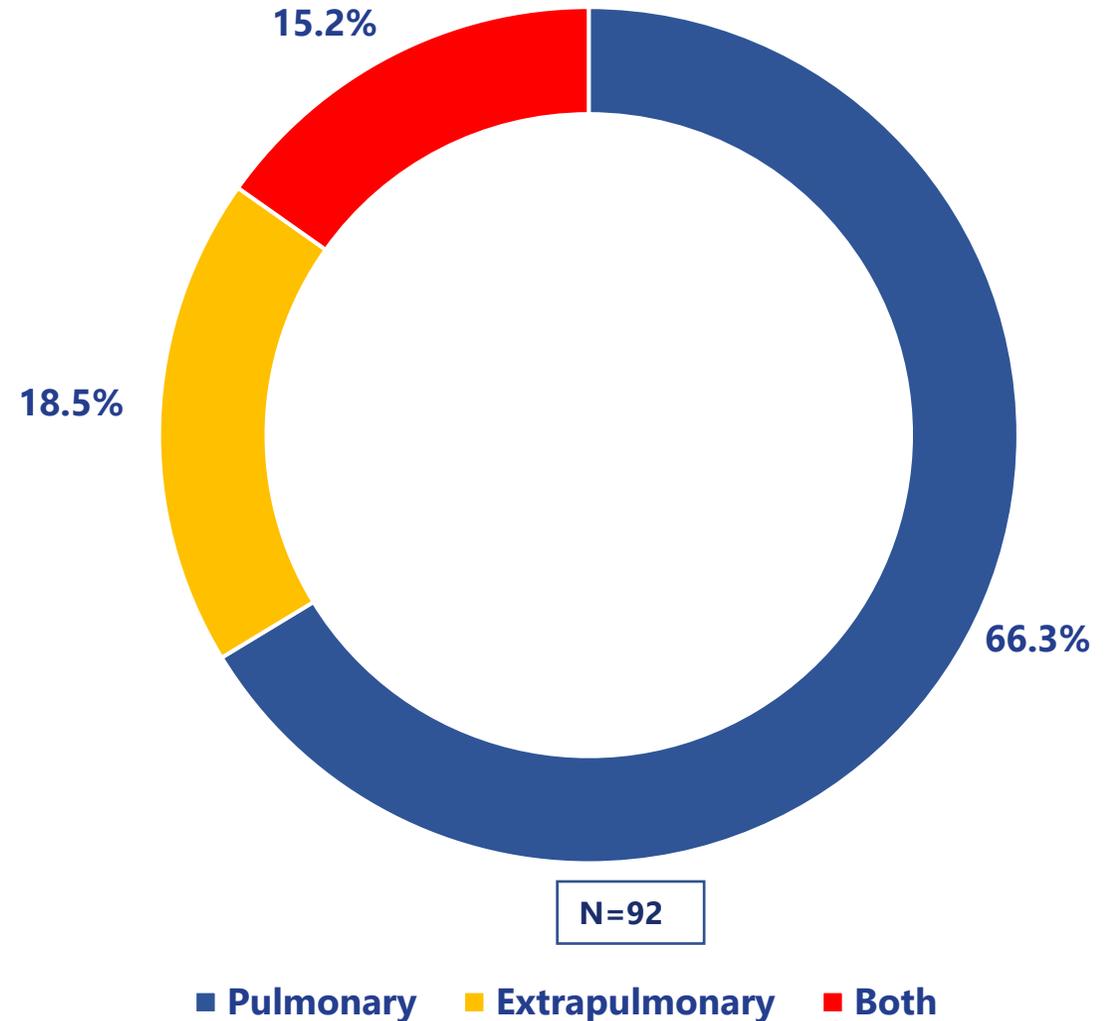
Screening for TB Infection

- Who is at risk / Who do we screen?
- How do we screen?
 - Tuberculin Skin Test (TST) or Quantiferon Release Assay
 - Both test for past exposure to TB
 - Both tests are only ~ 75% sensitive (25% false negative)
 - Neither test differentiates between active or latent ds.
- What evaluations are done with a positive screen?
 - History and physical exam
 - CXR
 - Sputum or tissue samples if suspicion of active disease

TB Cases by Site of Disease, Indiana, 2020

Extrapulmonary sites include:

- Lymphatic (38.1%)
- Bone and/or joint (23.8%)
- Eye and/or ear (9.5%)
- Genitourinary (9.5%)
- Peritoneal (4.8%)
- Breast (4.8%)
- Colon (4.8%)
- Spinal Cord (4.8%)



Latent TB Infection (LTBI)

- LTBI is the presence of *M. tuberculosis* infection *without* symptoms or radiographic evidence of TB disease (active TB).
- “Treatment of latent TB infection” replaces the terms “preventive” and “chemoprophylaxis”.
- Targeted tuberculosis testing is key to detect LTBI:
 - Groups at the *highest* risk for TB
 - “Decision to test is a decision to treat”

Persons at Higher Risk for Exposure to or Infection with TB

- Close contacts of known or suspected TB
- Persons from high TB endemic areas
- Residents and employees of high-risk congregate settings
- Health care personnel (HCPs)
 - High-risk clients

Persons at Higher Risk for Exposure to or Infection with TB (continued)

- Medically underserved, low-income populations
- High-risk ethnic minority populations
- Children exposed to high-risk adults
 - Under age 4, poorly developed cellular immunity
 - More rapid rate of progression and severe disease in young
- Persons who inject illicit drugs

LTBI Treatment Regimens

- An optimal LTBI treatment is minimally toxic and as short as possible to enhance completion rates.
- Until recently, 6 – 9 months of INH monotherapy was recommended.
- Recommendations now give shorter alternatives:
 - 3 months once weekly INH plus rifapentine (3HP)
 - 4 months daily rifampin alone (4R)
 - 3 months daily INH plus rifampin (3HR)

LTBI is REPORTABLE to the Indiana Department of Health!

Stagg, Zenner, et al. 2014. Treatment of Latent Tuberculosis Infection: A Network Meta-analysis.
Ann Intern Med. 2014;161(6):419-428

Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020.
MMWR Recomm Rep 2020;69(No. RR-1):1–11.



LTBI Treatment Regimens

Latent Tuberculosis Infection Treatment Regimens

Treatment regimens for latent TB infection (LTBI) use isoniazid (INH), rifapentine (RPT), or rifampin (RIF). **CDC and the National Tuberculosis Controllers Association preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy.**

Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), coexisting medical conditions (e.g., HIV*), and potential for drug-drug interactions.

https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w

	DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
Preferred	ISONIAZID [†] AND RIFAPENTINE ^{††} (3HP)	3 months	Once weekly	12	Adults and children aged ≥12 yrs INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg; 300 mg 14.1–25.0 kg; 450 mg 25.1–32.0 kg; 600 mg 32.1–49.9 kg; 750 mg ≥50.0 kg; 900 mg maximum Children aged 2–11 yrs INH [†] : 25 mg/kg; 900 mg maximum RPT ^{††} : See above
	RIFAMPIN [§] (4R)	4 months	Daily	120	Adults: 10 mg/kg; 600 mg maximum Children: 15–20 mg/kg; 600 mg maximum
	ISONIAZID [†] AND RIFAMPIN [§] (3HR)	3 months	Daily	90	Adults INH [†] : 5 mg/kg; 300 mg maximum RIF [§] : 10 mg/kg; 600 mg maximum Children INH [†] : 10–20 mg/kg [‡] ; 300 mg maximum RIF [§] : 15–20 mg/kg; 600 mg maximum
Alternative	ISONIAZID [†] (6H/9H)	6 months	Daily	180	Adults Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
			Twice weekly [¶]	52	
		9 months	Daily	270	Children Daily: 10–20 mg/kg [‡] ; 300 mg maximum Twice weekly: 20–40 mg/kg [‡] ; 900 mg maximum
			Twice weekly [¶]	76	

*For persons with HIV/AIDS, see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV available at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview>.

[†]Isoniazid is formulated as 100-mg and 300-mg tablets.

^{††}Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.

[¶]Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication).

[§]Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.

[‡]The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers. ^{Source:} American Academy of Pediatrics.

[‡]Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:629–53.

[¶]The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.



<https://www.cdc.gov/tb/topic/treatment/pdf/LTBITreatmentRegimens.pdf>

Current Challenges with Supply of Rifamycins

Rifamycins – Recent FDA investigations of many classes of medications for nitrosamine contamination (potential carcinogen). Levels in rifamycins have not met the threshold for recall, but the FDA is still working with manufacturers to lower levels.

As a result, supplies have been short at times for this drug class, including:

- **Rifampin** – Still recommended part of active and LTBI regimens if you are able to identify the supply needed

Current Challenges with Supply of Rifamycins (continued)

- **Rifapentine** – FDA concerns on top of already short supplies, but if supplies can be obtained it is still recommended as part of 3HP LTBI regimen (weekly INH/Rifapentine for 3 months, 12 doses)
- [Link to CDC's Division of TB Elimination September 2020 dear colleague letter with update on Rifamycin issues](#)
- Please contact your **regional nurse consultant** for supply updates or any additional questions!

Reporting LTBI

- LTBI is a reportable condition in the state of Indiana per State Code 410 IAC 1-2.5-111
 - “All newly diagnosed cases of LTBI shall be reported to the local health officer or the department within five business days.”
- Local health departments can report LTBI cases directly in the National Electronic Disease Surveillance System (NBS)
- Providers can access a reporting form [at this link](#).
 - Completed forms can be sent directly to the applicable local health department

Reporting LTBI continued

- Questions on reporting
 - Reach out to Indiana Department of Health TB Control Program
 - Phone: 317-233-7434
 - E-mail: tbcontrol@isdh.in.gov

Thank You!

Questions?

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References

- <https://www.cdc.gov/tb/topic/treatment/ltbi.htm#:~:text=CDC%20and%20the%20National%20Tuberculosis%20Controllers%20Association%20%28NTCA%29,rifapentine%20%283HP%29%20Four%20months%20of%20daily%20rifampin%20%284R%29> Accessed Sept 2020
- https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w#F1_down Accessed Sept 2020